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Phase II study of oral JAK1/JAK2 inhibitor ruxolitinib in advanced relapsed/refractory Hodgkin lymphoma

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ABSTRACT

JAK2 constitutive activation/overexpression is common in classical Hodgkin lymphoma, and several cytokines stimulate Hodgkin lymphoma cells by recognizing JAK1-/JAK2-bound receptors. JAK blockade may thus be therapeutically beneficial in HL.

This Phase II study assessed the safety and efficacy of ruxolitinib, an oral JAK1/2 inhibitor, in relapsed/refractory Hodgkin lymphoma patients. The primary objective was overall response rate according to IHP 2007 criteria.

Thirty-three advanced patients (median prior lines: 5; refractory: 82%) were included; nine (27.3%) received at least 6 cycles of ruxolitinib and six (18.2%) > 6 cycles therapy. The overall response rate after 6 cycles was 3/32 (9.4%) patients, all partial responders, with transient stable disease in 11/32. Best overall response rate was 6/32 (18.8%). Rapid alleviation of B-symptoms was commonly noted. Median response duration was 7.7 months, median progression-free survival 3.5 months (95%CI: 1.9-4.6), and median overall survival 27.1 months (95%CI: 14.4-27.1). Forty adverse events were reported in 14/33 patients (42.4%); one led to treatment discontinuation; 87.5% recovered without sequelae. Twenty-five were of $\geq$ Grade3. The latter consisted mostly of anemia (n=11) all considered related to ruxolitinib. Other main causes of $\geq$ Grade3 adverse events included lymphopenia and infections. Of note, there was no Grade4 neutropenia or thrombocytopenia observed.

Ruxolitinib shows signs of activity, though short-lived, beyond simple anti-inflammation. Its limited toxicity suggests the potential of being combined with other therapeutic modalities. *ClinicalTrials.gov: NCT01877005*

INTRODUCTION

Hodgkin's lymphoma (HL) is regarded as a curable malignancy in most cases, yet treatment failure still occurs in about 10% of early-stage disease[1]. In advanced-stage disease, up to 10% of cases do not reach complete remission (CR) and are thus considered primary refractory HL[2], while 20-30% of primary responders eventually relapse following first-line treatment[3].

For most patients with relapsed or refractory HL (R/R HL), the standard of care consists of high-dose salvage chemotherapy followed by autologous stem-cell transplantation (ASCT). For patients who experience R/R HL within 1 year of ASCT, the prognosis proves extremely poor, with a median survival time of 1.2 years[4]. For patients failing all classical approaches, new strategies including checkpoint inhibitors targeting PD-1 or antibody-drug conjugates targeting CD30 have become part of our therapeutic armamentarium against R/R HL[5-8]. However, patients with multiple relapses or who develop refractory disease remain in medical need, especially those failing brentuximab vedotin (BV) and PD-1 blockers

Classical HL is characterized by the presence of Hodgkin and Reed-Sternberg (HRS) cells and their variants[9]. HRS cells were demonstrated to shape their environment by secreting immunosuppressive cytokines and chemokines[10]. With this in mind, the Janus kinase (JAK) STAT pathway appears to be a relevant cytokine-induced signal transduction pathway shown to directly transfer signals from cell surface cytokine receptors to the cell nucleus. Given that enhanced JAK-mediated signaling was demonstrated in a significant number of HL patients[11], this signaling pathway has become a focus for developing novel therapeutic agents for the disease. Van Roosbroeck *et al.* reported JAK2 to be translocated in several cases of HL[12], with JAK inhibition shown to decrease the proliferation of cell lines. Whereas

such translocations are relatively rare, 9p24.1 genomic amplification including the *JAK2* locus appears common in HL, along with increased protein expression and activity, resulting in the constitutive activation of STAT6, an essential messenger of tumor cell growth [13-15]. In corollar, JAK 1/2 inhibition may be suitable to target the constitutive activation caused by either *JAK2* translocation or *JAK2* amplification and to impact the reactive microenvironment which contributes to HL growth via aberrant cytokine production[16].

Ruxolitinib is the first potent, selective, and oral inhibitor of JAK1/2 being developed for clinical use[17]. Its major effects include inhibition of proliferation, induction of apoptosis, and reduction in cytokine plasma levels, all mediated by the drug's ability to inhibit JAKs' capability to phosphorylate signal transducer and activator of transcription (STAT)[18]. In myelofibrosis, ruxolitinib exhibited durable efficacy in reducing splenomegaly and alleviating constitutional symptoms, and patients exhibited weight gain and improvement in their general physical condition[19]. The dose-limiting toxicity was thrombocytopenia, fairly-well managed via dose reduction or brief treatment interruption. In the present phase II study, we sought to investigate the safety and efficacy of ruxolitinib in patients with R/R HL. Exploratory biomarker analyses pertaining to plasma cytokine profiles and aberrations of *JAK2* were also carried out.

METHODS

Patient Eligibility

Patients aged 18 years or older with a diagnosis of R/R HL were eligible for entering the trial after having receiving at least one prior therapy, and for whom no treatment with proven efficacy was available, provided that they had measurable nodal disease

at baseline (≥1 cm in the longest transverse diameter, clearly measurable in at least two perpendicular dimensions) on computed tomography (CT) or magnetic resonance imaging (MRI), as well as an Eastern Cooperative Oncology Group (ECOG) performance score of ≤3. Additional inclusion criteria were absolute neutrophil count (ANC) ≥1.0 x 10^9/L, platelet count ≥75 x 10^9/L, serum creatinine ≤1.5 x upper limit of normal (ULN), serum bilirubin ≤1.5 x ULN, and ALT and AST levels ≤2.5 x ULN or ≤5.0 x ULN in the event the transaminase enhancement was due to HL-related liver disease. Pregnant or lactating patients were not allowed to be included into the trial, and men and women of childbearing potential had to agree to employ an adequate contraceptive method during the study treatment. Patients were permitted to have an undefined number of prior therapy lines, and prior allogeneic SCT was likewise allowed provided that patients had not received any immunosuppressive therapy within 90 days prior to starting the screening procedures. Patients were required to display a life expectancy of ≥3 months.

Study Design and Treatment

This multicenter, open-label, Phase II study (HIJAK, NCT01877005) was conducted at 10 LYSA centers in France and Belgium, with patients recruited from July 2013 through December 2014. Its primary efficacy endpoint was overall response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR), at 6 months of treatment by investigator assessment based on the revised response criteria for malignant lymphoma (Cheson 2007)[20]. Secondary objectives included B symptoms relief, best ORR (occurring at any time during study), duration of response (DOR), progression-free survival (PFS), overall survival (OS), as well as the incidence and severity of adverse events (AE).

The study was carried out in line with the ethical principles of the Helsinki Declaration and in compliance with the International Conference on Harmonization Guideline for Good Clinical Practice. The protocol was approved by the institutional review board of each study site and written informed consent was obtained from all patients.

Starting dose of ruxolitinib was 20mg given twice daily during six 28-day cycles for the induction period, if platelet count >200 x 10^9/L. Ruxolitinib dose was diminished to 15mg twice daily for patients with platelet counts between 75 and 200 x 10^9/L. Patients who achieved at least stable disease (SD) at the end of cycle 6 and for whom, according to the Investigator's opinion, a clinical benefit was observed were eligible for continuing ruxolitinib (15mg or 20mg), defined as a “maintenance”. Treatment could be pursued for up to 2 years or until progressive disease (PD), intolerability, or as long as the investigator sought that there was clinical benefit.

Study drug administration could be stopped for any Grade ≥3 non-hematological toxicity, with the exception of deep venous thrombosis and alopecia. Following event resolution to Grade $\leq$1, ruxolitinib could be resumed, with a 5 mg dose reduction and a maximum delay of 4 weeks. Mandatory dose decreases or interruptions for hematological toxicity as well as rules for permanent discontinuation are detailled in Supplementary Appendixes. Growth factors were allowed as per ASCO guidelines and infectious prophylaxis as per the guidelines of Heine *et al* [21].

Study Assessments

Baseline assessments comprised documentation of disease-related symptoms, physical examination, laboratory tests, and imaging studies of the neck, chest, abdomen, and pelvis, using CT or magnetic resonance imaging (MRI). Biopsy prior to inclusion was recommended, though not mandatory. Tumors were measured at

baseline, at the end of every two cycles, and following the six-cycle induction, as well as during maintenance therapy. Given the exploratory nature of the study, there was no centralized review of CT response. However, PET of the responders were all centrally reviewed by a nuclear physician (ASC) to confirm partial or complete metabolic response based on Deauville five-point scale. The evaluable set for efficacy was restricted to patients who had received at least 28 days of the study drugs.

Safety was monitored up to 1month post-treatment. AEs were summarized by means of the Medical Dictionary for Regulatory Activities, and graded using the National Cancer Institute's (NCI) Common Terminology for Adverse Events, Version 3.0. Laboratory abnormalities were assessed according to the NCI-CTCAE Version 4.0. Only Grade 3 or 4 toxicities and Grade 2 infections were to be reported. All patients were included in the toxicity analysis.

Exploratory Biomarker Analysis

Blood samples (5mL) were taken at baseline prior to drug administration and on Cycle 2, Day 1, for the measurement of 27 cytokines related to the immune system using bead-based immunoassays (L.K.). Analysis of JAK2 gains, amplifications, and gene rearrangements was also performed (H.A.P.) using fluorescent *in situ* hybridization (FISH) with 2 tri-color sets of probes associating *JAK2*/9p24 break-apart probes with a control centromeric probe (*CEP9/*9q21): the already prepared probes from Empire genomics on one hand, and the association of the JAK2 B/A probe from Kreatech with the CEP9 probe from Vysis on the other hand. The *CD274*/*PDL1* and *PDCD1LG2/PDL2* loci at 9p24 were studied with home-made prepared bacterial artificial chromosome (BACs) probes purchased from the Chori BACPAC Resources

Center (Oakland). Extraction, labelling and hybridization were performed on paraffin embedded tissue, as previously reported.[22]

Statistical Methods

The sample size in this Phase II study was calculated using an exact single-stage Phase II design[23], along with the following hypothesis. A two-stage design with interim analysis for activity or toxicity was not planned given the very advanced stage of the patient, with relative paucity of alternative options, and the potential toxicity of ruxolitinib that was expected to be in the low range, based on myelofibrosis data. The treatment was considered ineffective if the ORR was ≤15%, and effective if ORR ≥35%. Under the assumption of an alpha first-order risk error set at 5% and beta at 20% with one-sided test, it was deemed necessary to include a total of 28 evaluable patients with a cut-off number of eight. If at least eight patients displayed an ORR, the hypothesis ORR ≤15% was rejected with a target error rate and an actual error rate of both 0.05. If seven or less patients displayed an ORR, the hypothesis ORR ≥35% was rejected with a target error rate of 0.2 and an actual error rate of 0.187. The ORR estimate and its 90% confidence intervals (CI) were calculated for all patients who completed at least one study drug cycle.

The Kaplan-Meier method was employed to estimate the median value and its 95% CI for TTR, DOR, PFS, and OS. The safety set comprised all patients who received at least one study drug. All statistical analyses were performed using the SAS software, Version 9.2. *P*-values <0.05 were considered statistically significant. All available data was included in data listings and tabulations, with no imputations of values for missing data conducted. An interim analysis was neither planned nor performed.

RESULTS

Patient Disposition and Characteristics

Patient characteristics are listed in Table 1. From July 2013 to December 2014, a total of 33 patients with R/R HL were recruited. Median age was 37 years (range, 19-80), patients mostly had advanced HL (Stage III/IV), and were heavily pretreated, with a median number of five prior regimens including ASCT (54%), allo-SCT(15%), and BV (82%). Of the patients, 27 (82%) had refractory disease HL. Among the 33 patients, 22 had biopsy-confirmed relapse of HL. Among the six patients displaying response, a biopsy at relapse was performed in five of them 8 days, 12 days, 6 weeks (n=2) and 14 months prior to inclusion.

Patient Drug Exposure

The median number of ruxolitinib cycles administered was 4, ranging from 1 to 12 (Table 2). Among the patient population, nine received all planned six cycles, of whom six continued on maintenance therapy with ruxolitinib. The remainder discontinued ruxolitinib therapy, for the most part due to PD, and owing to AEs in one patient.

Response and outcome

The patient disposition is illustrated in Fig. 1. Among the 33 HL patients included into the trial, one patient did not complete the first cycle owing to PD and was thus not included in the efficacy analysis. ORR at the end of the ruxolitinib induction period (6 months) was 3/32 (9.4%; 90% CI: 2.6-22.5%), all being PRs. Best ORR at any time throughout induction was 6/32 (18.8%; 95% CI: 7.2-36.4%), all PRs. A detailled

analysis of responders characteristics is provided in Table 3. Fig. **2** and **3** illustrate metabolic evolution in 2 patients. Interestingly, UPN 611001, who had achieved PR after 6 cycles, eventually converted into CR during follow-up, beyond the six cycles. Achievement of complete metabolic response was confirmed by central review. At the time of writing, two patients (UPN 611001 and 881001) are still taking ruxolitinib. Fig. 4 displays change in target tumour measurement in individual patients. If any, best reduction at any time throughout treatment was taken.

In addition, during 6-month induction, transient stable disease was recorded in 11 patients, though of limited duration. Overall, the disease control rate (thus including SD with CR and PR) was 53.1% (n=17/32), (95%CI : 34.7-70.9%] of a median duration of 1.9 month.

The alleviating effect on systemic symptoms, such as pruritus, fever, and sweating, was noteworthy, starting within the first month of drug administration and commonly lasting. The impact was the most remarkable on the control of pruritus, which affected 35.5% of patients prior to initiating therapy but only 6.6% after the first ruxolitinib cycle. Sweating, which was present in 32.2% of the patients at inclusion, was reduced to 20% after one cycle. Fever was abolished in 3/4 patients presenting this symptom at inclusion.

The median follow-up was 17.5 months. As illustrated in Fig. **5**, median PFS was 3.5 months (95% CI: 1.9-4.6). Median duration of response was 7.7 months (95% CI: 1.8-NA) for the six patients who eventually achieved response (not shown). Overall, 30 patients displayed PD, with 97% at the initial site and/or 60% at new sites. Following ruxolitinib discontinuation, 25 (83.3%) patients were given further treatments, consisting of chemotherapy in 19, and immunotherapy in nine, the latter comprising rituximab in four, BV in three, and nivolumab in two. Transplantation was

eventually carried out in five patients, consisting of allogenic SCT in four and ASCT in the remaining one. Among the 25 patients prescribed further therapy, the CR and PR rates observed were 10 and 15%, respectively. Overall, twelve patients died on account of lymphoma progression (83.3%), toxicity of other treatments (8.3%), or other reasons (8.3%). Median OS was 27.1 months (95% CI: 14.4-27.1).

Safety

All patients enrolled into the study received at least one dose of study medication and were thus included into the safety set. A total of 40 AEs was observed in 14/33 patients (42.4%). In 6 patients, AEs were related to ruxolitinib. In eight of them, AEs were of $\geq$ grade3 (Table 4A). Among the 40 AEs recorded, 30 (75%) occurred during induction, 35 (87.5%) recovered without sequelae, 18 (45%) were related to ruxolitinib. There was no drug-related death recorded, one AE resulted in permanent drug discontinuation, while 87.5% of AEs recovered without sequelae. Characteristics and grade of AEs by system organ class and preferred terms are displayed in Table 4B. Twenty-five (62.5%) were of $\geq$ Grade3. The latter consisted mostly of anemia (n=11) all considered related to ruxolitinib. Other main causes of $\geq$ Grade3 AE included lymphopenia (n=4), infections (n=3) and miscellaneous causes. Of note, there was no Grade4 neutropenia or thrombocytopenia observed.

Eight serious AEs (SAEs) were reported in four patients, either during induction (n=5), maintenance (n=1) or after end of treatment (n=2). These SAEs consisted of infection in three patients, namely device-related sepsis, gastroenteritis, and lung infection. The other SAEs were anemia, diarrhea, subdural hematoma, bone pain, and pulmonary embolism. Two SAEs (anemia, lung infection) were deemed drug-related and six were considered Grade ≥3: infection (n= 3), anemia, subdural

hematoma, and pulmonary embolism. Of the eight SAEs, six recovered without sequelae, while device-related sepsis and pulmonary embolism, observed in the same patient, persisted until the patient died owing to PD and were thus not considered as the cause of death. Among the 33 patients, one second primary malignancy was observed (colic adenocarcinoma in 80-year old male patient).

Biomarker analysis

Using bead-based immunoassays, plasma levels of 27 cytokines related to the immune system were measured at baseline and after cycle 1. At baseline, there was no difference in cytokine levels between responders and non-responders, as defined by Cheson 2007 criteria. In responders, the only cytokine that significantly decreased was CX-CL10 (P.01). In patients presenting with pruritus (n=11), PDGF-BB (Supplemental Appendixes), IL-5, IL-10, IL-12, IL-13, IL-17, eotaxin, FGF basic, MIP1b, rantes, and VEGF were significantly increased. In the latter patients, ruxolitinib treatment significantly decreased PDGF-BB, IL-10, IL-12, IL-13, IL-17, FGF basic and VEGF. Among the patients who were analyzable for JAK2 amplification in HRS cells (n=12), polysomy (suggesting hyperdiploidy) was detected in all of them, and specific *JAK2* amplification in only one. The latter patient achieved PR by CT-scan criteria and also PET-scan response lasting 4 months. It is noteworthy that the *PDL1* and *PDL2* loci (which are in the vicinity of the JAK2 locus at 9p24) analysed by FISH with BAC probes showed the same pattern of gains as for the JAK2 locus.

DISCUSSION

JAK/STAT activation, driven by an aberrant network of cytokines and chemokines in the HL microenvironment, is critical for the proliferation and survival of neoplastic

HRS cells[24,25]. JAK/STAT pathway also plays a role in immune evasion by HL cells via secretion of chemokines leading to Th2 homing or via the regulation of PD-L1/L2 expression, which confer immune privilege to HRS cells. Chromosome 9p24.1/PD-L1/PD-L2 alterations increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and their further induction through JAK/STAT signaling[26-28]. This complex crosstalk between malignant HRS cells and the reactive microenvironment could be targeted to overcome chemoresistance. Based on this rationale, we explored JAK 1/2 inhibition in a phase II study of fixed dose ruxolitinib in advanced HL patients before the onset of the PD-1 blockers era. With 9.4% ORR at the end of the 6-month induction, this study did not reach its primary efficacy goal. Still, when including transient responses seen before the 6-month evaluation, ORR was 18.8% in some heavily pretreated patients, most of whom where refractory and had failed treatment with BV. These responses were sometimes durable (median=7.7 months). Some other patients had disease control, but with uncertain clinical benefit. A notable finding to be highlighted was the B symptoms and pruritus relief, which was quick and long-lasting, resulting in a number of patients being reluctant to discontinue the compound, even despite PD. Thus, the latter effect should not be interpreted as a proven surrogate of anti-lymphoma activity.

Despite mitigated, these results tend to support the concept of JAK1/2 inhibition as a potential therapeutical mean in HL. There is presently only scarce data available on ruxolitinib use in the HL indication. In a preliminary report of an ongoing study, Kim *et al* showed rapid achievement of disease control (1CR, 5PR, 1SD) out of 13 advanced HL patients treated with ruxolitinib at 20 mg bid.[29] Younes *et al* reported changes in tumour measurements in HL patients treated in a phase I study by SB1518, an inhibitor of JAK2 and FLT-3.[30] *In vitro*, AZD1480, an inhibitor of JAK1

and JAK2 kinases, could regulate proliferation in HL cell lines[27]. The multikinase lestaurtinib also showed growth inhibition and apoptotic increment in HL cell lines and HL cells from lymph nodes[31]. Finally, a clinical grade JAK2 inhibitor fedratinib inhibited cHL cell lines proliferation in a *JAK2* copy number-dependent manner implying decreased phosphorylation of STATs and expression of downstream targets including PD-L1 showing immunomodulation by JAK inhibitors[32].

If JAK2 is actually an appropriate target, questions arise as to why the study outcome was not more convincing. Could the drug's limited activity be attributed to insufficient dosage? Given that we observed unambiguous cytokine profile changes and frequent B symptoms improvements, it would seem that the dosage of 2x20mg was appropriate, a dosage at which target inhibition occurs in myelofibrosis[33]. Another factor possibly influencing the outcome was the stage of our patients, represented by the high percentage of refractoriness. At this late stage, the genetic changes would be so complex that selective inhibition of JAKs is insufficient in cells dependent to other signaling pathways to promote their survival, thus further curbing the study's potential. It is known that genomic aberrations, such as chromosome breakpoints, are more numerous in HL later clinical stages[34]. Resistance mechanisms to JAK/STAT inhibition have been reported such as a feedback loop of paradoxically activated extracellular signal-regulated kinases 1 and 2 (ERK1/2)[27]. Aberrations of the 9p24.1 amplicon, which contains the *JAK2* gene, are more frequent with advanced disease[28]. Surprisingly, in our patients, *JAK2* amplification was seen at a much lower incidence, suggesting a lower proportion of patients harboring the target of ruxolitinib, but this should be taken with caution since not all patients could be analyzed. It remains that our panel maybe qualified for Jak2 target on a limited extent.

With respect to safety, ruxolitinib was by and large well-tolerated, with no drug-related mortality reported. The most prominent toxicities included drug-related anemia and manageable infectious events with no specific pattern. The relative lack of hematological toxicity suggests that combination with genotoxic compounds could be feasible. For patients having discontinued ruxolitinib therapy, a switch to chemotherapy and/or immunotherapy was feasible, suggesting that the compound does not jeopardize further treatment.

The question now remains as to how this compound can best be utilized in the future. The exploratory nature of our study does not allow identifying best candidates on the basis of the clinical stage or biomarkers results. The cytokine profile displays changes in patients with pruritus, but the latter are not correlated with clinical response. *JAK2* status could be explored in a minority of patient, though the only patient with *JAK2* amplification achieved a response. It will be important to focus on biomarkers results in ongoing studies of JAK inhibition in HL. Given its limited benefits as monotherapy, combination may possibly enhance its therapeutic potential. Ruxolitinib, which has no overlapping toxicity with chemotherapy, has been combined with hypomethylating agents, lenalidomide, and even intensive chemotherapy.[35-38] *In vitro* data have shown that ruxolitinib could restore sensitivity of cisplatin-resistant cell lines with higher Jak2 expression[39]. Interestingly, the combination of BV with ruxolitinib resulted in additive and synergistic killing in a xenograft mouse model of HL through a mechanism involving mitochondrial control of apoptosis[40]. Another means to boost ruxolitinib's potential would be the combination with agents blocking other signaling pathways. Interestingly, the combination of ruxolitinib with a Bcl2/Bcl-xL inhibitor displayed dramatic synergy in an adult T-cell leukemia cell line via a mechanism implying BAX activation[41]. Finally, the effect of

combining chemical JAK blockade and anti-PD1/L1 strategy should be analyzed in HL, keeping in mind, however, that a potential antagonism may be encountered due to these two drugs acting on the same target, given that PD1-L1 expression is dependent on JAK2 activity.

In conclusion, based on a strong biological rationale for clinical evaluation of JAK2 blockade in HL, we initiated a phase II study of ruxolitinib in R/R HL patients. The study failed to fulfill the efficacy criteria for further development of the drug as monotherapy. Nonetheless, ruxolitinib showed hints of activity that surpasses solely anti-inflammatory activity in very advanced patients. This may suggest that further improvements will come from a more complete inhibition of signaling pathways implied in HRS cell survival or from combination with chemotherapy, such as BV.

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TABLES

Table 1 Demographics and patient characteristics

Demographics and patient characteristics	All patients *N* = 33
Gender, n (%)	
Male	21 (63.6%)
Female	12 (36.4%)
Age in years, median (range)	37.0 (19.0-80.0)
ECOG	
0	11 (33.3%)
1	15 (45.5%)
2	5 (15.2%)
3	2 (6.1%)
Ann Arbor stage	
I	1 (3.0%)
II	7 (21.2%)
III	3 (9.1%)
IV	22 (66.7%)
B symptoms	
Yes	16 (48.5%)
No	17 (51.5%)
Extranodal involvement	
Bone	13 (39.4%)
Liver	6 (18.2%)
Lung	12 (36.4%)
Soft tissues	4 (12.1%)
Time since initial diagnosis in months, median (range)	55.4 (8.7 – 216.1)
Prior therapies	
Prior lines, median (range)	5 (1 – 16)
Chemotherapy	33 (100%)
Radiotherapy	18 (54.5%)
Brentuximab vedotin	27 (82%)
ASCT	18 (54.5%)
Allogeneic transplantation	5 (15.2%)
Interval since last treatment in months, median (range)	6 (1.1 – 75.0)
Disease status at inclusion	
Relapse	6
Refractory	27 (81.8%)

ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group.

Table 2 Treatment exposure and modifications

Treatment exposure and modifications	All patients *N* = 33
Cycles given, number, median (range)	4 (1-22)
Received full induction (6 cycles), %	9 (27.3%)
Received maintenance (> 6 cycles), %	6 (18.2%)
Percentage of planned dose[1]	
<75%	3 (9.1%)
(75%-90%)	4 (12.1%)
(90%-110%)	25 (75.8%)
(110%-125%)	1 (3.0%)
Dose modification	
Yes	20 (60.6%)
Type of modification[2]	
Dose reduction	2 (10.0%)
Dose interruption	18 (90.0%)
Dose increase	3 (15.0%)
Number of interrupted days interruption if any, median (range)	4 (1 – 28)

[1]Defined as follows: (total number of tablets taken/total expected number of tablets) *100, taking into account protocol-defined dose reduction.
[2]The total sum of the percentages for the type and the reasons of modification may be greater than 100.0% as a patient may specify several types of modification and reasons for treatment modification

Table 3 Characteristics of responders (best response achieved during 6-month ruxolitinib induction)

UPN	**Prior treatment**		**Extranodal involvement**	**Response (Cheson 2007)**
	N	Type		
611001	9	ABVD, BEACOPP, MINE, IGEV, GVD, CAELYX, GVD, RT, BV	Liver	PR*,[1]
211004	8	ABVD, RT, IVA, transplantation, MINE, GVD, BV, ASHAP	Breast	PR
601001	5	BEACOPP, DHAP, IGEV, transplantation-RT, BV	Liver, bone, lung	PR
601004	5	ABVD, DHAP, RT, RT, BV	None	PR
641001	1	ABVD[2]	None	PR
881001	5	ABVD, transplantation, MINE, BV, GEMOX	Lung	PR[1]

*Patient eventually achieved CR during maintenance

[1]Patients still under treatment by ruxolitinib at the time of writing ; [2]Patient with morbid obesity not eligible for standard approaches with chemo/immunotherapy.

UPN, unique patient number ; RT, radiotherapy ; BV, brentuximab vedotin

Table 4 Treatment-emergent adverse events (AEs)

A. Patients with AE (*N* = 33)

Treatment-emergent adverse events[1]	All patients *N* = 33
Patients with ≥ 1 AEs	14 (42.4%)
N AE/patient, median (range)	2 (1-11)
N patients with AE ≥ grade 3	8 (24.2%)
Patients with AE related to ruxolitinib	6 (18.2%)
Patients with AE leading to drug discontinuation	1 (3%)
Patients with AE leading to death	0 (0%)

[1]Total number of AE, 40

B. Characteristics of AEs (*N* = 40) by system organ class and preferred terms

AE, *n* (%)	Any grade	Grade 2	Grades ≥ 3
Any AE	40	15	25
Infections and infestations	13	10	3[1]
Anemia	11	0	11
Lymphopenia	4	0	4
Thrombocytopenia	2	0	2
Weight decreased	1	0	1
Respiratory and thoracic disorders	3	2	1
Diarrhoea	1	1	0
Infuenza-like illness	1	1	0
Subdural hematoma	1	0	1
Bone pain	1	1	0
Epilepsy	2	0	2

[1]Implantable device infection, gastro-enteritis, lung infection

FIGURE LEGENDS

Fig. 1 Patient disposition.
*N months on maintenance therapy: 4, 6, 6, 21, 16, 22;
PD: progressive disease.

Fig. 2 Response after ruxolitinib.

Illustrative patient (UPN 601004). (A) PET-CT frontal view. (B) PET-CT sagital view. PR with allievation of B symptoms and blood inflammation was achieved 2 months after starting ruxolitinib. At month 6, the patient was slowly progressive but did refuse to stop ruxolitinib.

CRP, c-reactive protein

Fig. 3 Response after ruxolitinib.

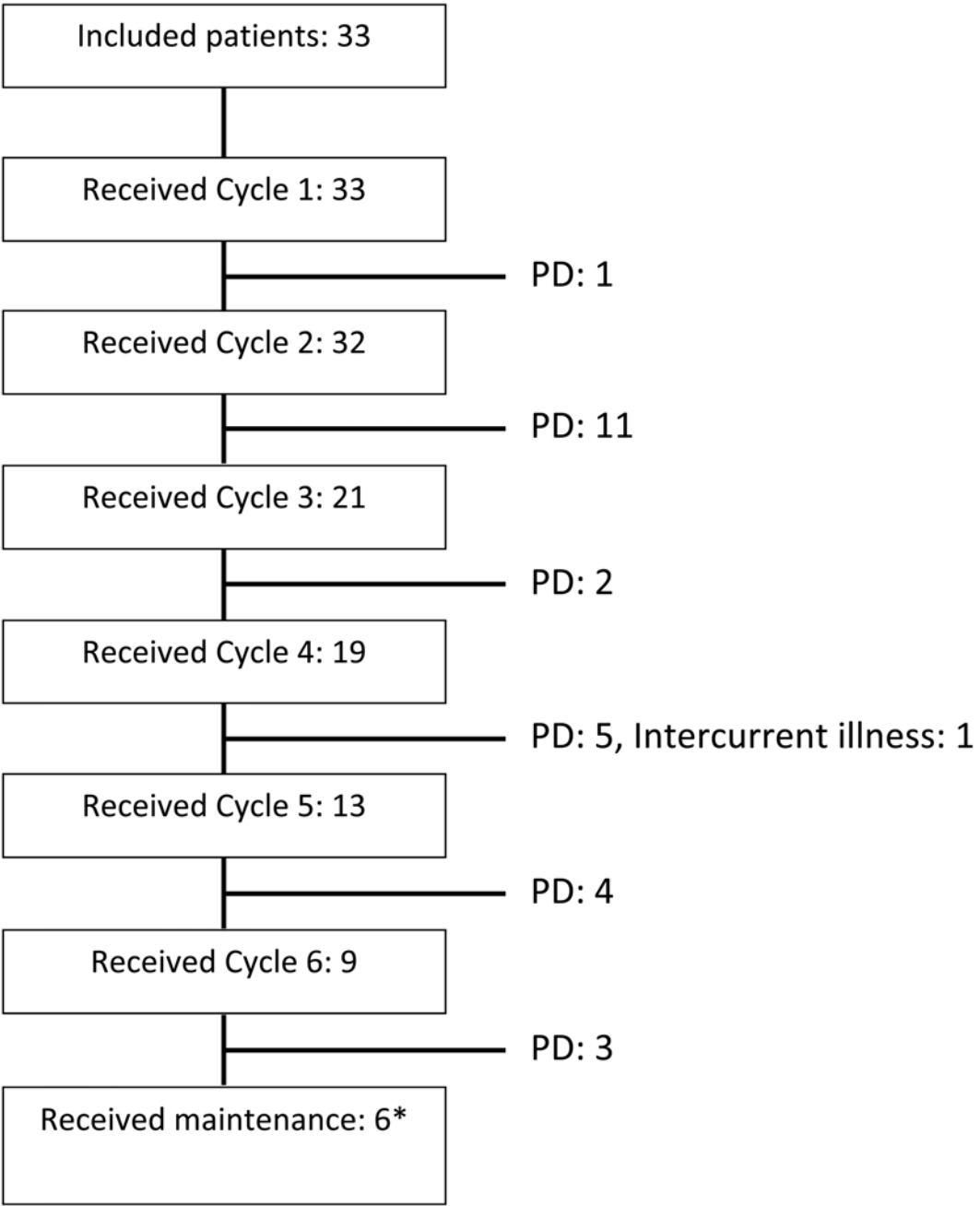
Illustrative patient (UPN 601001). Comparison of frontal PET-scan prior to inclusion and after 2 months of ruxolitinib. There was a rapid improvement of constitutional symptoms after a few days on ruxolitinib. PET after 2 months showed metabolic PR with on a total volume reduction of tumoral lung lesions of 64%.

Fig. 4 Waterfall plot demonstrating percent change from baseline in target tumor dimensions (best response, n=27). Of note, among the 32 patients evaluable for disease response, 5 had no end-of-treatment SPD measurements by CT scan as planned by protocol because there were obvious signs of disease progression.

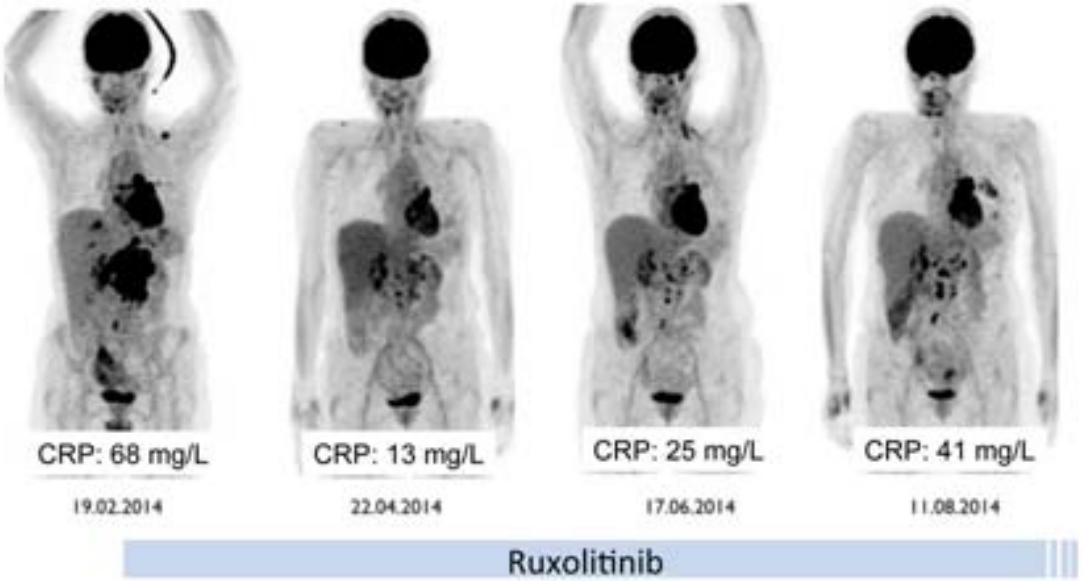
*Persisting positive PET scan, considered as PR

Fig. 5 Kaplan-Meier estimates of overall survival and progression-free survival in 32 evaluable patients with Hodgkin lymphoma receiving ruxolitinib.

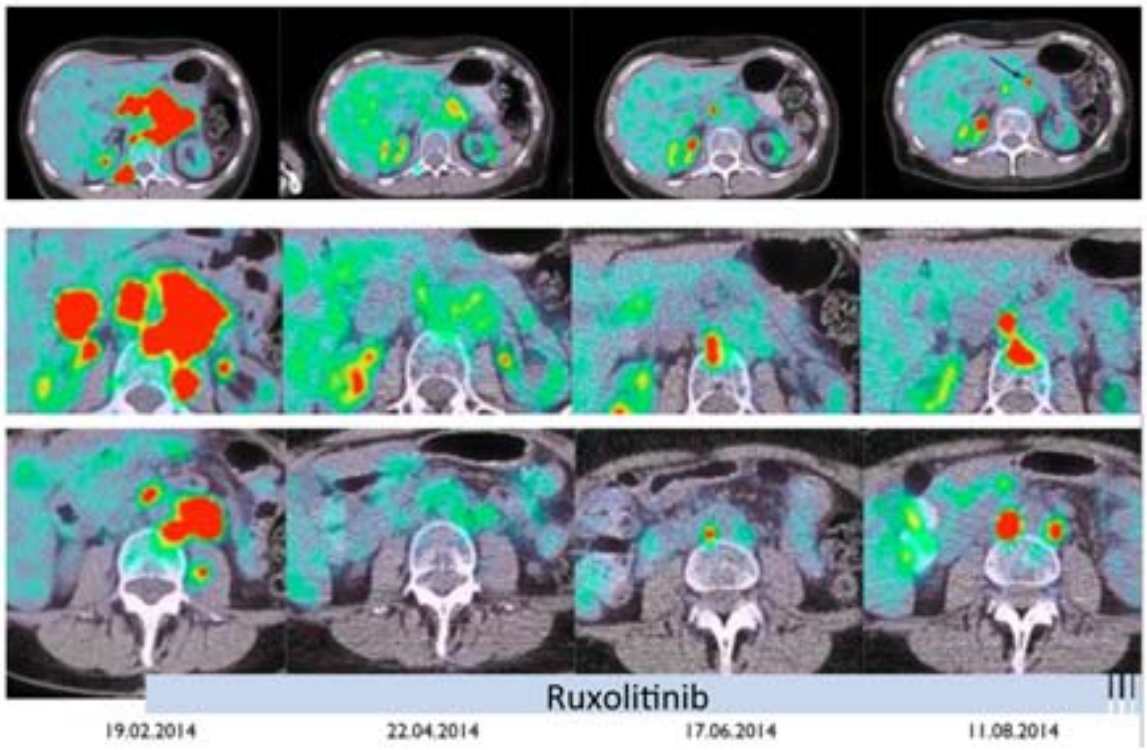
(A) Progression-free survival. (B) Overall survival.


Included patients: 33
Received Cycle 1: 33
PD: 1
Received Cycle 2: 32
PD: 11
Received Cycle 3: 21
PD: 2
Received Cycle 4: 19
PD: 5, Intercurrent illness: 1
Received Cycle 5: 13
PD: 4
Received Cycle 6: 9
PD: 3
Received maintenance: 6*

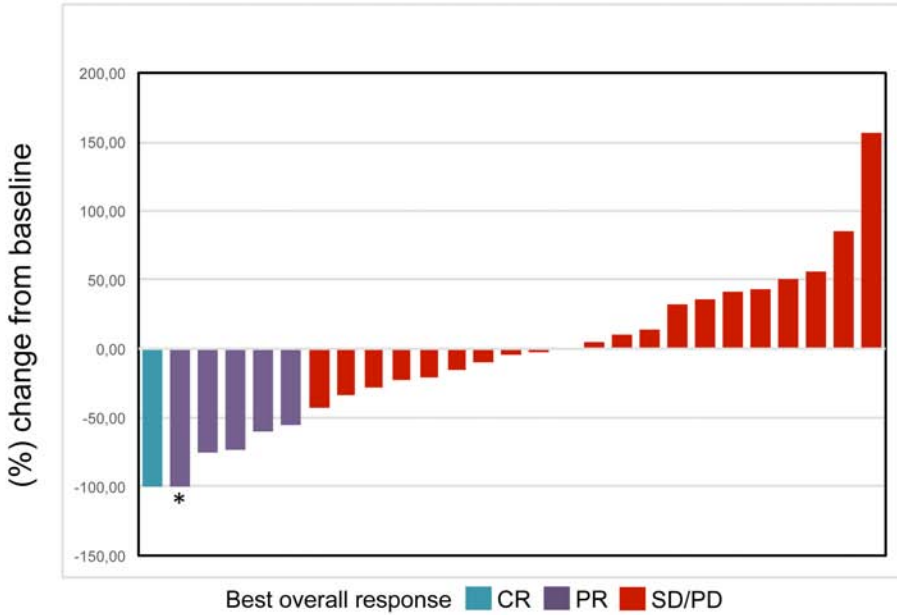
A.

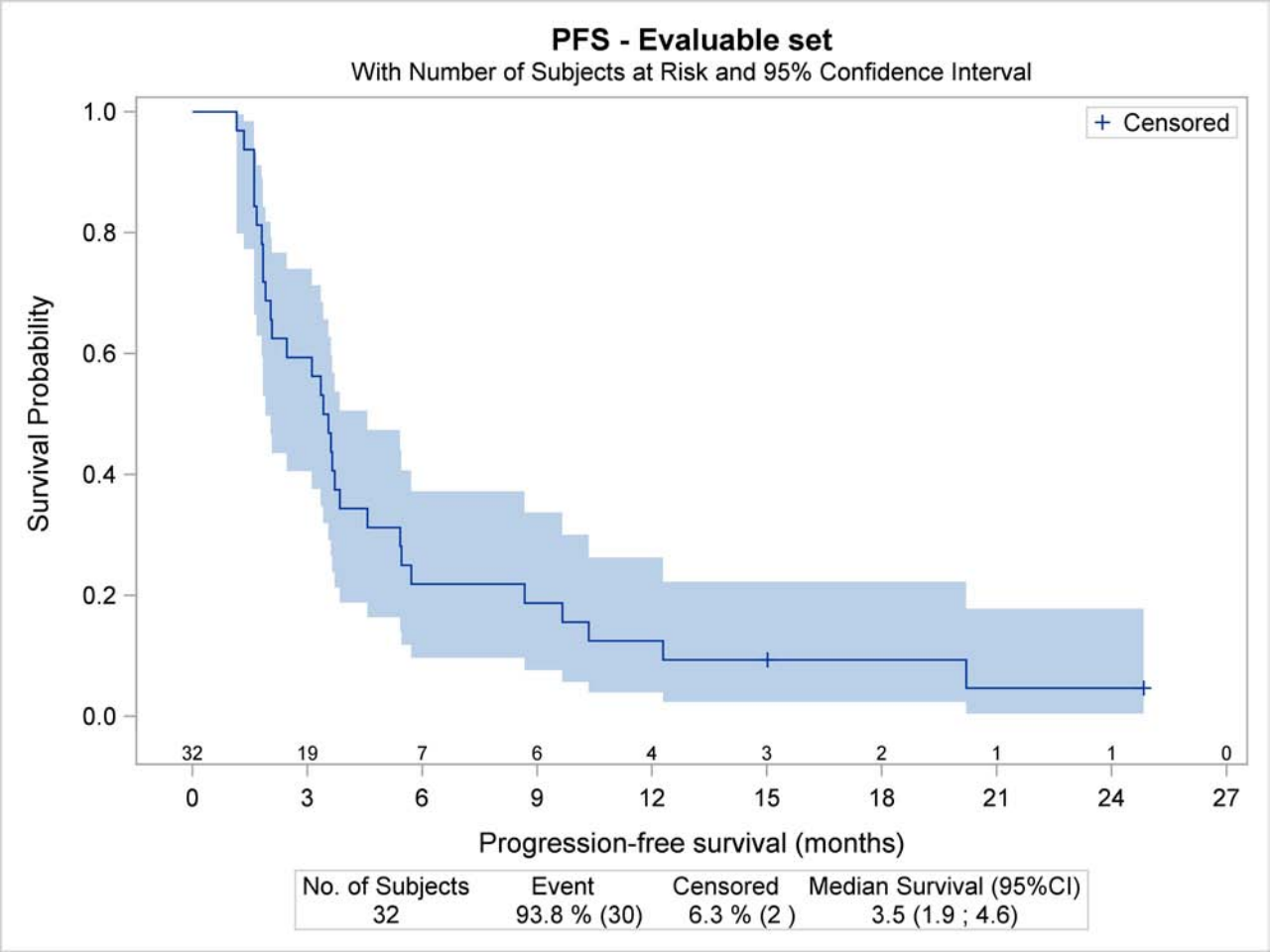

CRP: 68 mg/L
CRP: 13 mg/L
CRP: 25 mg/L
CRP: 41 mg/L
19.02.2014
22.04.2014
17.06.2014
11.08.2014
Ruxolitinib

B.


Ruxolitinib
19.02.2014
22.04.2014
17.06.2014
11.08.2014


Ruxolitinib
04/10/2013
05/12/2013


200,00
150,00
100,00
50,00
0,00
-50,00
-100,00
-150,00
(%) change from baseline
*
Best overall response
CR
PR
SD/PD


PFS - Evaluable set
With Number of Subjects at Risk and 95% Confidence Interval
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
32 19 7 6 4 3 2 1 1 0
0 3 6 9 12 15 18 21 24 27
Progression-free survival (months)
No. of Subjects | Event | Censored | Median Survival (95%CI)
32 | 93.8 % (30) | 6.3 % (2) | 3.5 (1.9 ; 4.6)

Hijak study by E. Van Den Neste *et al*

Supplementary data:

Mandatory dose decreases or interruptions for hematological toxicity:

There are mandatory dose decreases or interruptions for declining platelet count or ANC level while on ruxolitinib therapy. Dosing must be held if platelet count decline below 25 x 109 /L, or if ANC falls below 0.5 x 109 /L. Patients with platelets below 50 x 109 /L and/or ANC below 0.5 x 109 /L should be followed biweekly.
The dose reduction strategy for platelet count is depicted in Table 1 This table takes into account doses that might be present after a prior dose reduction. Ruxolitinib dose will not be adapted to lymphocytes count.

Table 1 : dose reduction strategy for low platelet count

Platelet count at time of decline	Dosing at the time of platelet decline			
	20 mg BID	15 mg BID	10 mg BID	5 mg BID
	Dose that MUST be instituted			
≥ 75 x 10^9/L	No dose reduction required			
50 to < 75 x 10^9/L	10 mg BID	10 mg BID	10 mg BID	5 mg BID
25 to < 50 x 10^9/L	5 mg BID	5 mg BID	5 mg BID	5 mg BID
< 25 x 10^9/L	MUST stop dosing			

Restarting or re-instituting previous dose

Dosing may be restarted following recovery of platelet count and/or ANC to acceptable levels. ANC level recovery to above 500/µL but less than 750/µL will allow dosing to be restarted at 5 mg BID. ANC level between 750 and 1000/µL may restart at 10 mg BID. Increase of ANC above 1000/µL will allow a further dose increase to the initial dosing (15 mg BID or 20 mg BID).

Table 2: Restarting or increasing ruxolitinib dose after safety interruptions or dose reductions for low ANC count

Current ANC level	Recommendation
< 0.5 x 10^9/L	Continue hold
0.5 to < 0.75 x10^9/L	5 mg BID for at least one week; if stable, may increase to 10 mg BID
0.75 to < 1 x 10^9/L	10 mg BID for at least one week; if stable, may increase to 15 mg BID
≥ 1 x 10^9/L	15 mg BID. If stable for at least one week, increase to 20 mg BID for patients who were initially at 20 mg BID

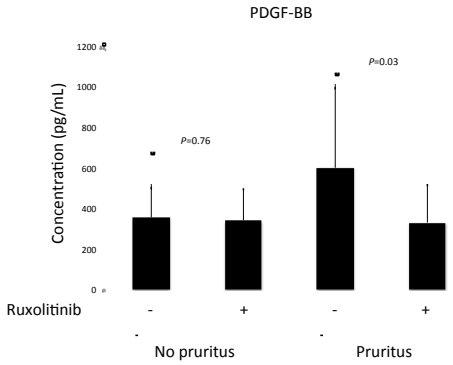
Table 3: Restarting or increasing ruxolitinib dose after safety interruptions or dose reductions for low platelet count

Current platelet level	Recommendation
< 25 x 10^9/L	Continue hold
25 to < 50 x 10^9/L	5 mg BID for at least one week; if stable, may increase to 10 mg BID
50 to < 75 x 10^9/L	10 mg BID for at least one week; if stable, may increase to 15 mg BID
≥ 75 x 10^9/L	15 mg BID. If stable for at least one week, increase to 20 mg BID for patients who were initially at 20 mg BID

Rules for permanent discontinuation

If the study drug is interrupted for any reason for more than 4 weeks, dosing may not be restarted. Study drug must be permanently discontinued if the lowest allowed dose (5 mg BID, or 5 mg QD with concomitant CYP3A4 inhibitor) is not tolerated due to the following: platelet count cannot be maintained > 25 x 109 /L, ANC cannot be maintained > 0.5 x 109 /L. Study drug must also be permanently discontinued due to the following: > grade 3 clinical event after re-challenge with the drug. Exceptions NOT requiring study withdrawal are fatigue, insomnia, obesity, constitutional symptoms (disabling but not life-threatening), salivary gland changes, arthritis, and joint effusion.

Cytokines



PDGF-BB concentration in patients with (n=8) or without (n=17) pruritus before treatment (-) and after one cycle of ruxolitinib (+).